Diet, Tobacco Use, and Fatal Prostate Cancer: Results from the Lutheran Brotherhood Cohort Study

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ABSTRACT

A cohort of 17,633 white males age 35 and older responded to a mailed epidemiological questionnaire in 1966 and was followed until 1986 to determine the risk of cancer associated with diet, tobacco use, and other factors. During the 20-year follow-up, 149 fatal prostate cancer cases were identified. Relative risks for prostate cancer were significantly elevated among cigarette smokers (relative risk, 1.8; 95% confidence interval, 1.1–2.9) and users of smokeless tobacco (relative risk, 2.1; 95% confidence interval, 1.1–4.1). No significant associations were found with frequency of consumption of meats, dairy products, fruits, or vegetables. There were no overall significant associations between consumption of vitamin A from animal sources (retinol) and provitamin A from plant sources (carotene) and risk, but positive trends were seen for ages under 75, while inverse associations were found at older ages. Beverage consumption, including drinking coffee and alcohol, was unrelated to risk. Marital status, education, rural/urban status, and farming residence were also unrelated to the risk of fatal prostate cancer. The findings add to limited evidence that tobacco may be a risk factor for prostate cancer, but fail to provide clues to dietary or other risk factors.

INTRODUCTION

Prostate cancer is a major form of cancer among men, accounting for 20% of cancer incidence and 11% of cancer deaths in the United States (1). Worldwide, the highest rates of prostate cancer occur among United States blacks and the lowest among Asians (2). Despite its high incidence and mortality, very little is known about the etiology of prostate cancer. Previous epidemiological studies have suggested a number of risk factors, including socioeconomic and marital status, farming residence, alcoholic beverages, exposure to cadmium, venereal disease, number of sexual partners, and androgen levels (3–5). A few investigations have linked cigarette smoking (6–8) to an increased risk of prostate cancer, but this tumor is generally not considered to be tobacco related (9, 10).

The role of diet in the etiology of prostate cancer has been investigated in a number of studies with equivocal results. Increased intake of fat and animal products has been associated with increased risk (11–14), although not always consistently (15–17). Some investigators have found increased dietary intake of vitamin A to enhance prostate cancer risk, particularly at older ages (17–20), while others have reported that high serum levels of retinol (21) and consumption of β-carotene-containing foods lower the risk (22, 23). In this report, we present results from a cohort study of 17,633 men to determine associations of diet, tobacco use, beverage consumption, and demographic characteristics with the risk of fatal prostate cancer. Such a study design permits the measurement of diet and other factors

before the diagnosis of cancer, thus avoiding recall bias, a potential problem in case-control studies of cancer.

MATERIALS AND METHODS

The Lutheran Brotherhood Cohort. In 1966, a cohort ($n = 26,030$) of white male policy holders of the Lutheran Brotherhood Insurance Society who were at least 35 years of age was selected for a mortality follow-up study (median age at entry into the cohort, 51). In September 1966, a questionnaire was mailed to members of the cohort with questions on demographic background, frequency of use of dietary items, and tobacco habits. A response rate of 68.5% was achieved after three mailings. A comparison of respondents and nonrespondents, using original insurance records, found little difference in age, urban/rural residence, or policy status (24).

Since the LBS[2] cohort was a self-selected group, having purchased life insurance, several characteristics of the cohort members were different from those of the United States population. The cohort was primarily from the upper midwest, particularly Minnesota, and northeastern areas of the United States (45 and 39%, respectively), with 30% of Norwegian and other Scandinavian heritage. In addition, compared to United States white males in the mid-1960s, the LBS cohort was more rural (37 versus 29%), and more were farmers (38 versus 4%) (25).

Mortality. The LBS cohort was followed for mortality from 1966 to 1986, for a total of 286,731 person-years. Death certificates, which were received semiannually from the Lutheran Brotherhood Insurance Society, were coded for underlying cause of death, all other contributory causes of death, and all other significant conditions by the nosologist of the Minnesota State Department of Health. During the 20-year follow-up, 4513 deaths, including 1033 cancer deaths, were identified. The two major causes of death were heart disease and cancer. Among the cancer deaths, the distribution of anatomic sites was similar to that among United States males, with the most common being malignancies of the lung ($n = 203$), prostate ($n = 149$), and large intestine ($n = 120$). The overall mortality experience of this cohort was similar to that of United States white males, although the number of prostate cancer deaths was slightly lower than expected (standard mortality ratio, 0.92) (26). During the follow-up, 4027 subjects (23%) were lost to follow-up due to lapsed policies or discontinuation of policies after premium maturity. A comparison of cancer mortality at 11.5 years of follow-up showed no significant differences between original respondents and nonrespondents and those whose policies lapsed (24).

Tobacco and Alcohol. Information on tobacco use, including the use of cigarettes, pipes, cigars, and smokeless tobacco (snuff or tobacco chewing), was elicited in the 1966 questionnaire. Since no subsequent information on tobacco use was obtained, smoking exposure in the analysis pertained to the smoking experience of cohort members in 1966. Thus, current smokers were defined as those smoking in 1966. Information on the use of beer and whiskey was also asked in the 1966 questionnaire; persons who used either beer or liquor (whiskey, gin, cognac, etc.) at least 6 times a year were defined as users.

Dietary Data. The respondents were asked about the frequency of their current (in 1966) monthly intake of foods. Thirty-five individual food items, including vegetables (potatoes, cabbage, rutabagas, carrots,

[2] The abbreviations used are: LBS, Lutheran Brotherhood Insurance Society; RR, relative risk; CI, confidence interval.

cauliflower, corn, green salads, tomatoes, peas, and beans), vegetable and fruit soups, fruits (oranges, apples, grapes, bananas, canned fruit), fruit juices, fish, meat, dairy products (milk and ice cream), cereals, bread, and alcohol were included in the questionnaire. These 35 food items were combined into 9 food groups. Information on portion size (sex specific) and nutrient values was derived from the Second National Health and Nutritional Examination Survey and from data of the United States Department of Agriculture, respectively (27–28). For example, the carotene value for a specific food item for each subject was derived by multiplying the reported consumption frequency by the average portion size and the carotene content of that food item. The total carotene index for a specific individual was derived by summing the values from all carotene-containing foods.

One hundred eighty-five individuals were excluded because they had more than 10 unknown responses to the food item questions. The excluded individuals were older, more likely to reside in rural areas, and less educated as compared to the 17,633 subjects who remained in the final analysis. For the included subjects, 71% had no missing data on any food items; of the remaining 29% (87% of whom had fewer than 5 items missing), we imputed intake for missing food items, using the median values of the remaining subjects, stratified by urban/rural, education, and age categories. The imputation is unlikely to greatly affect the nutrient analysis, since, for example, it contributed to only about 1% of the vitamin A index. Consumption of food groups and nutrients was divided into quartiles based on the intake of all 17,633 subjects.

Statistical Analysis. A Poisson regression program for modeling hazard functions with grouped data was used to calculate age-adjusted relative risks (29–30). Since the number of prostate cancer deaths in this cohort is small relative to the size of the cohort, the prostate cancer deaths occurring during the 20-year follow-up may be regarded as statistically independent Poisson variables. As with other grouped survival analyses, the major assumption for this Poisson regression method is that the hazard function is constant in each time interval. Five-year age intervals (attained age) were used for the grouping of the data; RRs for prostate cancer were calculated for each age stratum and summarized over all strata for the selected variables. Persons-years for study subjects were accumulated up to death, loss to follow-up, or the end of the follow-up in 1986.

RESULTS

Among the 149 cohort members who died of prostate cancer, the median age at death was 73, compared to 70 for all deaths in the cohort. There were no significant associations for prostate cancer risk with marital status, farming residence, or education.

Table 1 shows the risk of fatal prostate cancer associated with intake of 9 food groups. No significant associations were found with consumption of meat, poultry, fish, eggs, dairy products, vegetables, cruciferous vegetables, fruits, or breads. In addition, no individual food item was found to increase or decrease risk significantly.

No significant trends in risk were found in association with total vitamin A, retinol, or β-carotene intake. The smoking-adjusted RRs for the 4 quartiles were 1.0, 1.2, 0.8, and 1.1 for total vitamin A; 1.0, 0.8, 0.9, and 1.2 for retinol; and 1.0, 1.2, 1.3, and 0.9 for β-carotene; however, because increased intake of vitamin A and/or carotenes has been reported to enhance the risk among older men (age at diagnosis ≥70), intake of total vitamin A, retinol, and β-carotene was analyzed for the two age groups separately (age at death <75 or ≥75) (Table 2). For age <75, increased consumption of total vitamin A enhanced the risk of prostate cancer: smoking-adjusted RRs for the four quartiles were 1.0, 2.3, 1.7, and 2.8, respectively. However, for older ages, increased consumption of total vitamin A was associated with a decreased risk of prostate cancer; RRs

Table 1 *Relative risks of fatal prostate cancer by quartile levels of selected food groups in the Lutheran Brotherhood cohort, 1966–1986*

Food groups (times/mo)[a,b]	No. of deaths	RR[c]	95% CI
Meat			
<17	50	1.0	
18–26	35	0.9	0.6–1.4
27–39	37	1.1	0.7–1.6
>39	27	0.8	0.5–1.3
Poultry			
<0.5	14	1.0	
0.5–1.5	65	1.5	0.8–2.6
1.6–4.0	50	1.1	0.6–1.9
>4.0	20	0.9	0.4–1.8
Fish			
<0.8	31	1.0	
0.8–1.7	51	1.1	0.7–1.6
1.8–4.0	39	0.9	0.6–1.4
>4.0	28	0.8	0.5–1.3
Eggs			
<4.0	41	1.0	
4.0–9.0	40	0.8	0.5–1.3
9.1–21.0	45	1.2	0.8–1.8
21.1–37.5	23	0.9	0.5–1.5
Dairy			
<26	46	1.0	
27–51	47	1.2	0.8–1.8
52–85	33	0.8	0.5–1.3
86–189	23	1.0	0.6–1.7
Vegetables			
<56.8	48	1.0	
56.9–75.9	30	0.8	0.8–1.8
76.0–99.1	45	1.2	0.8–1.8
>99.1	26	0.7	0.4–1.2
Cruciferous vegetables			
<1.2	32	1.0	
1.2–2.2	34	1.1	0.7–1.8
2.3–4.5	42	1.2	0.8–2.0
>4.5	41	1.3	0.8–2.0
Fruits			
<29.3	37	1.0	
29.3–46.5	34	0.9	0.5–1.4
46.6–67.0	40	1.0	0.6–1.5
>67.0	38	0.9	0.6–1.4
Breads			
<88	27	1.0	
88–138.8	41	1.2	0.7–1.9
138.9–167.3	49	1.5	0.9–2.4
>167.3	32	1.0	0.6–1.6

[a] Consumption frequency per month.
[b] Food items included in each food group are as follows: meat: beef, bacon, fresh pork, and smoked ham; poultry: chicken; fish: fresh fish, salted fish, and fish balls; dairy group: milk and ice cream; vegetables: potatoes, green salad, tomatoes, carrots, peas, corn, beans, vegetable soup, cabbage, cauliflower, pea soup, and rutabaga; cruciferous vegetables: cabbage, cauliflower, and rutabaga; fruits: fruit juice, canned fruit, apples, bananas, oranges, grapes, and fruit soup; bread group: bread, packaged cereal, cooked cereal, pancakes, and flat bread.
[c] Adjusted for age and tobacco use.

were 1.0, 0.7, 0.5, and 0.4, respectively. There were similar risk patterns by age for retinol and β-carotene. Similar age effects were found when 70 (age at death) was used as the cutoff.

All forms of tobacco use were associated with an increased risk of prostate cancer (Table 3). Risks were significantly elevated among persons who ever used any form of tobacco (RR = 1.8, 95% CI, 1.1–2.9), both among cigarette smokers and users of smokeless tobacco. Risks according to number of cigarettes smoked and regularity of smokeless tobacco use are presented in Table 4. There was no clear dose response for amount of cigarettes smoked, and there was little difference after adjustment for the use of smokeless tobacco. Among current smokers, however, the risk was elevated among those who inhaled compared to those who did not (RR = 2.0; 95% CI, 0.7–5.8). Among persons who had ever used smokeless tobacco, the risk was highest among persons who dipped snuff or chewed tobacco regularly (RR = 2.4; 95% CI, 1.3–4.9), as compared to those who had never used any tobacco.

A review of contributory and other causes of death on the

Table 2 *Relative risks[a] of fatal prostate cancer, by age and quartile levels of nutrient indices in the Lutheran Brotherhood Cohort, 1966–1986*

Quartiles[b]	Total vitamin A[c]	Retinol	β-carotene
Age < 75[d] (n = 78)[e]			
1 (low)[f,g]	1.0	1.0	1.0
2	2.3 (1.1–4.9)	1.1 (0.5–2.3)	1.2 (0.6–2.5)
3	1.7 (0.8–3.8)	2.0 (1.0–3.8)	1.6 (0.8–3.1)
4	2.8 (1.4–5.8)	1.7 (0.9–3.3)	1.9 (1.0–3.7)
	P[h] < 0.05	P < 0.05	P < 0.05
Age ≥ 75 (n = 71)[e]			
1 (low)	1.0	1.0	1.0
2	0.7 (0.4–1.3)	0.6 (0.3–1.2)	1.1 (0.6–2.1)
3	0.5 (0.3–1.0)	0.4 (0.2–0.8)	1.1 (0.6–1.9)
4	0.4 (0.2–0.9)	0.9 (0.5–1.7)	0.2 (0.1–0.6)
	P < 0.01	P > 0.05	P < 0.01

[a] Adjusted for age and tobacco smoking.
[b] Cutoff points for quartile were 95,289, 128,007, and 167,479 IU/month for total vitamin A; 9,585, 13,672, and 19,084 Retinol Equivalent/month for total retinol; and 11,517, 19,100, and 30,165 μg/month for β-carotene.
[c] Represents vitamin A from both plant and animal sources.
[d] Age at death for prostate cancer cases.
[e] Number of prostate cancer deaths.
[f] Reference category.
[g] Number of prostate cancer deaths by quartile, among those age <75 were 10, 23, 17, and 28 for total vitamin A; 14, 15, 27, and 22 for retinol; and 13, 16, 22, and 27 for β-carotene; among those age ≥75 were 29, 18, 13, and 11 for total vitamin A; 27, 17, 8, and 19 for retinol; and 20, 22, 25, and 4 for β-carotene. Number of study subjects among those age <75 were 3,252, 3,389, 3,384, and 3,389 for total vitamin A; 3,240, 3,328, 3,397, and 3,449 for retinol; and 3,424, 3,381, 3,316, and 3,293 for β-carotene; among those age ≥75 were 1,156, 1,019, 1,025, and 1,019 for total vitamin A; 1,168, 1,081, 1,011, and 959 for retinol; and 3,294, 3,369, 3,405, and 3,346 for β-carotene.
[h] Linear trend test.

Table 3 *Relative risks of fatal prostate cancer associated with tobacco use in the Lutheran Brotherhood Cohort, 1966–1986*

Tobacco use[a]	No. of deaths[b]	Cohort person-years	RR[c]	95% CI
Never used any tobacco	19	58,888	1.0	
Used any form of tobacco[d]	116	217,300	1.8	1.1–2.9
Pipes and/or cigars only	9	13,676	1.6	0.7–3.5
Cigarettes only	22	48,823	2.0	1.1–3.7
Smokeless tobacco[e] only	10	4,025	4.5	2.1–9.7
Cigarettes and pipes and/or cigars	35	93,544	1.7	1.0–2.9
Cigarettes and smokeless tobacco	8	7,613	2.9	1.3–6.5
Smokeless tobacco and pipes and/or cigars	4	2,729	1.4	0.5–4.1
Cigarettes and smokeless tobacco and pipes and/or cigars	16	22,896	1.6	0.8–3.1

[a] All categories refer to ever users.
[b] Missing data not included.
[c] Adjusted for age.
[d] Included 12 subjects who used some form of tobacco, but for whom no detailed information was available for further classification.
[e] Snuff and chewing tobacco.

Table 4 *Relative risks of fatal prostate cancer associated with level of tobacco use in the Lutheran Brotherhood Cohort, 1966–1986*

Tobacco use	No. of deaths[a]	Cohort person-years	RR[b]	95% CI
Cigarettes[c]				
Never used any tobacco	19	58,888	1.0	
Ever used cigarettes[d]	91	190,640	1.8	1.1–2.9
Occasional and ex-smoker	52	87,215	1.9	1.1–3.3
1–19 cigarettes/day	12	29,404	1.6	0.8–3.3
20–29 cigarettes/day	11	36,588	1.7	0.8–3.5
30 + cigarettes/day	3	15,732	1.4	0.4–4.4
Smokeless tobacco[f]				
Never used any tobacco	19	58,888	1.0	
Ever used smokeless tobacco[g]	42	41,716	2.1	1.1–4.1
Ex-users	13	14,117	1.8	0.8–3.9
Occasional	5	8,666	1.4	0.5–3.9
Regular	24	18,934	2.4	1.3–4.9

[a] Missing data not included.
[b] Adjusted for age.
[c] Thirty-four subjects who used pipes, cigars, and smokeless tobacco only were not included.
[d] Including some cigarette smokers who used other forms of tobacco.
[e] Snuff and chewing tobacco, 78 subjects who used only other forms of tobacco were not included.
[f] Adjusted for cigarette smoking.
[g] Including some smokeless tobacco users who used cigarettes.

current users of beer were 1.7 (95% CI, 1.0–2.9) and 1.2 (95% CI, 0.8–1.7), respectively, while the risk for ex- and current users of liquor were 0.7 (95% CI, 0.3–1.5) and 1.0 (95% CI, 0.7–1.4), respectively.

DISCUSSION

In contrast to some studies that have linked dietary fat and animal products with increased prostate cancer risk, we found no association with consumption of eggs, milk, pork, or beef. In addition, we found no positive effect upon prostate cancer risk with the intake of green vegetables. There also was no overall association with retinol or β-carotene intake. The observed higher risks among those under 75 years and lower risks among those 75 years and older for consumption of total vitamin A, retinol, and β-carotene stand in contrast to studies that reported increased risk with vitamin A intake in older men (17–20). The etiological implication of our findings on vitamin A or those of previous researchers are not clear at this time.

The lack of an association between dietary factors and the risk of prostate cancer may be due partially to the limited number and nature of the dietary items in the 1966 food-frequency questionnaire. The foods in the self-administered instrument in this study were adapted from dietary questionnaires of earlier case-control studies in Minnesota and Norway, which were specifically designed to elicit sufficient information to discriminate between persons with light and heavy consumption of these food items (31). However, because certain food items that are major contributors of vitamin A (both retinol and carotene) or dietary fat in the American diet (such as liver, cheese, butter, processed meat, broccoli, spinach, and cantaloupe) were not included in the questionnaire, we were unable to capture all sources for each nutrient. Hence there may be random misclassification of dietary intakes, which may tend to dampen the relative risk estimates but should not account for the opposite trends associated with vitamin A in men under versus over age 75.

In recent reviews of tobacco smoking and cancer (9, 10), prostate cancer is considered not to be a tobacco-related cancer. Most epidemiological studies, including 8 prospective studies (9) and 7 case-control studies (32–38), have reported no increased risk of prostate cancer among smokers. The lack of an

.death certificates revealed 58 subjects for whom prostate cancer was not the underlying case of death. The 58 cases were much older than the 149 fatal cases (median age at death 81 versus 73). In this group, a positive association with smokeless tobacco use was also found. Fourteen of the cases were regular users of smokeless tobacco (RR = 2.3; 95% CI, 1.0–5.2), including 8 who dipped snuff or chewed tobacco exclusively (RR = 2.5; 95% CI, 1.0–6.5). The risk associated with cigarette smoking in this group, however, was not significantly elevated (RR = 1.1; 95% CI, 0.5–2.3).

Risk of prostate cancer was also assessed for consumption of coffee and alcoholic beverages. For persons who drank 3–4 and 5 or more cups of coffee/day, the RRs were 0.8 (95% CI, 0.6–1.2) and 1.0 (95% CI, 0.6–1.6), respectively, as compared to those who drank less than 3 cups of coffee/day. Increased consumption of beer or hard liquor was weakly associated with an increased risk. Smoking-adjusted risks for ex-users and

association with cigarette smoking in these case-control studies could be due in part to the high prevalence of cigarette smoking in control groups because most used hospital patients as the comparison group and a moderate association with cigarette smoking may be masked by the prevalence of smoking in hospital controls. It is noteworthy that when neighborhood controls were used for comparison, a positive association with cigarette smoking was observed (7, 8). Cohort studies, however, do not have this potential methodological limitation, and all but the follow-up study of United States veterans (6) showed no excess of prostate cancer mortality among tobacco users. In the LBS cohort, risk was increased nearly 80% among smokers. The increase may have been more easily detected in this cohort, since the prevalence of current cigarette smoking (32%) was low compared to that of United States middle-aged white males in 1965 (44%) (39). We, however, found no evidence of dose-response trends, and it is possible that the base-line reference group of the nonusers of tobacco differed in other ways that relate to prostate cancer risk. If real, the association of cigarette smoking with prostate cancer could have a hormonal basis, since cigarette smoking is associated with an antiestrogenic effect (40, 41), and male smokers are reported to have elevated levels of circulating androsterone and testosterone (42, 43), which may increase the risk of prostate cancer. Further research is needed to clarify whether cigarette smoking is related to the risk of prostate cancer.

The prevalence of smokeless tobacco use in the LBS cohort was 17%, which is similar to the national prevalence (20%) reported in the 1960s (44). Although it is known that the use of smokeless tobacco is related to oral cancer, its relationship with other cancers is less clear (44). Various parts of the body may be exposed to components of smokeless tobacco, such as nitrosamines, via the blood stream. The amounts of certain tobacco-specific nitrosamines are greater in snuff than in cigarettes (45), and some N-nitroso compounds [N-nitrosobis(2-hydroxypropyl)amine and N-nitrosobis(2-oxypropyl)amine] can induce papillomas and squamous cell carcinomas of the prostate in rats (46, 47), while adenocarcinoma can be induced in both intact and castrated rats when testosterone is given along with N-nitrosobis(2-oxopropyl)amine (48). Our results suggest that the risk of prostate cancer associated with smokeless tobacco may be greater than that for cigarette smoking. However, we were unable to evaluate the intensity and duration of smokeless tobacco use because such information was not collected. Furthermore, the effect of tobacco chewing could not be separated from that of using snuff in this study, since the questionnaire inquired about their combined use. Consistent with other studies, the use of smokeless tobacco in the LBS cohort is more prevalent among farmers and persons who reside in rural areas. Although studies (37, 49) have reported an association of farming residence with prostate cancer, we found no increased risk among farmers or rural residents.

Although the study is prospective in design, information on dietary habits and tobacco use was obtained only once, in 1966. Misclassification of exposures thus could occur with those subjects who changed their tobacco or dietary habits in the follow-up period. For example, men who smoked in 1966 would still be classified as smokers, when as many as 40% of them may have quit smoking in the ensuing 20 years as they aged (39). Similarly, dietary patterns could have changed with time, and misclassification of dietary exposure is thus likely. However, such misclassification is likely to be nondifferential and would lead to an underestimation of the true effect.

Attrition is a major problem in most prospective studies. During the 20-year period, 4027 (23%) members of the cohort were lost to follow-up, due to lapsed policies or discontinuation of policies after premium maturity. We examined dietary intake, tobacco use, alcohol, and coffee consumption for these subjects lost to follow-up at 20 years relative to those remaining in the cohort and found no significant differences. In addition, after 11.5 years of follow-up, a special investigation of cancer mortality among lapsed and discontinued subjects found no difference from that of the remainder of the cohort (24). Thus, selection bias introduced by attrition in the study is likely to be minimal.

The LBS cohort is a self-selected group, with more farmers, rural residents, and individuals of Scandinavian descent than in the United States as a whole (25), perhaps limiting the generalizability of the results. In addition, because mortality is used in the study as the end point, it is probable that subjects who had a diagnosis of advanced prostate cancer are more likely to die of prostate cancer and be included in the study; thus the results may not generalize to the less invasive and aggressive types of prostate cancer.

In summary, our findings suggest that the use of cigarettes and smokeless tobacco is significantly associated with an increased risk of fatal prostate cancer, providing renewed incentive for evaluation of tobacco as a cause of this cancer. No significant relationships were found for dietary factors evaluated in the study, but the possible role of vitamin A and β-carotene deserves further attention.

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